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| 10/773,356 | 02/05/2004 | Leslie P. Weiner | 23714-07992 | 6800 |

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| EXAMINER | |
|---|---|
| EWOLDT, GERALD R | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/773,356 | WEINER ET AL. | |
| | Examiner | Art Unit | |
| | G. R. Ewoldt, Ph.D. | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10/18/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *8,9,12,14-19,23,26,28 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,9,12,14-19,23,26,28 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☑ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

**DETAILED ACTION**

1. Applicant's amendment, IDS, and remarks filed 10/18/07 are acknowledged.

2. Claims 8, 9, 12, 14-19, 23, 26, 28, and 30 are pending and under examination.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 30 stands rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

As set forth previously, The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, the recitation of:

A) The method comprising the specific steps set forth in Claim 30. Note: including the new steps of the 2/07/07 amendment.

A review of the example shows that Applicant has used some of the language of the example, but not all of it. For example, the first sentence of Example 1 discloses that it encompasses only a method of treating secondary progressive MS, yet the claim does not recite this limitation. Further, the Example discloses vaccination with $40 \times 10^6$ cells and vaccination intervals of 3 months or 6 weeks, limitations not found in the claim. Accordingly, the specification cannot support the method as claimed.

Applicant's arguments, filed 10/18/07 have been fully considered but they are not persuasive. Applicant argues that new amendments to the claim recite language from Example 1 of the specification and do not comprise the introduction of new matter.

Again, Applicant has included some of the limitations found in the example but has excluded other. Specifically, the claim

excludes cell culture expansion employing 50U/ml IL-2. In step d) a 10-14 day time period has been excluded. In step e) repeating steps c) and d) weekly has been excluded. Additionally, the limitation of step f) comprising the reduction of aberrant autoimmune T cells has not been found in the example.

5. Claims 8, 9, 12, 14-19, 23, 26, 28, and 30 are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

As set forth previously, The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) … T cells are cultured in the presence of whole bovine myelin proteins or synthetic human proteins … (Claims 8 and 30).

B) … T cells that respond to a plurality of different myelin proteins (Claim 11).

C) … T cells are reactive to a plurality of different myelin proteins (Claim 23).

Regarding A), Applicant cites page 8 of the specification for support.

At page 8 the specification discloses PBMCs are cultured in the presence of cow myelin proteins or synthetic complete human proteins.

Regarding B) and C), Applicant cites pages 8 and 11 of the specification for support.

At page 8 the specification discloses PBMCs are cultured in the presence specific myelin antigens. Page 11 discloses a specific example in which PBMCs and myelin antigens are employed.

As set forth previously, The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, "T cells … prepared by selecting and expanding human T-cells that respond to a plurality of different myelin proteins …".

Applicant cites original Claims 11 and 13, and pages 8 and 11 of the specification in support.

A review of the cites does not reveal T cells prepared by the claimed method. As set forth previously, the specification discloses the culturing of PBMCs and not just T cells.

Applicant's arguments, filed 10/18/07 have been fully

considered but they are not persuasive. Applicant cites page 8, line 4 and "numerous points in the specification".

Again, the specific limitations of the claims have not been found anywhere in the specification. While the specification may disclose vaccines comprising T cells, the method of making the vaccine comprising T cells recited in the claims employs PBMCs.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 8, 9, 12, 14-19, 23, 26, 28, and 30 stand rejected under 35 U.S.C. 103(a) each as being unpatentable over Stinissen et al. (1996) in view of Correale et al (1995) and the background teachings of the specification.

As set forth previously, Stinissen et al. teaches a method of mediating an immune response comprising administering subcutaneously irradiation-attenuated T-cells derived from autologous peripheral mononuclear cells (comprising T cells) cultured in the presence of natural or synthetic human myelin proteins (see particularly page 503, T CELL VACCINATION IN MS).

The reference differs from the claimed invention only in that it does not teach the use of attenuated T cells that target more than one myelin protein and in that it does not teach the optimization of the claimed method as set forth in dependent Claims 16-19.

Correale et al. extends the teachings of Stinissen et al. regarding additional MS autoantigens. The reference teaches that as MS develops, myelin breakdown exposes additional myelin antigens (besides MBP) to autoreactive T cells, thus, broadening the autoimmune response (see particularly page 1375, last paragraph - page 1376, first paragraph. The reference further teaches the use of bovine brain as a source of myelin proteins (see particularly page 1371, column 2).

The background (Description of the Related Art) section of the specification further supports the teachings of Correale et al. See, for example, page 2 wherein the specification discloses "Presently, the myelin proteins thought to be the target of an immune response in MS include myelin basic protein (MBP), proteolipid protein (PLP), myelin associated glycoprotein (MAG), and myelin-

oligodendrocyte glycoprotein (MOG). Also there is an increasing body of evidence that the T-cell receptor has extraordinary flexibility, allowing it to react to many different proteins (Brock R., K.H. Wiesmuller, et al. (1996) Proc. Natl. Acad. Sci. (USA) 93:13108-13113; Loftus D.J., Y. Chen, et al. (1997) J. lmmunol. 158:3651-3658)." The specification additionally discloses, "In both EAE and MS, myelin basic protein (MBP), proteolipid protein (PLP), and MOG are thought to be the main target antigens for autoreactive T-cells (Brostoff S.W. and D.W. Mason (1984) J. Immunol. 133:1938-1942; Tabira and Kira, 1992). Myelin associated glycoprotein (MAG) may be important in MS but does not produce EAE in experimental models."

From the teachings of the references it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform the method of administering attenuated T cells, as taught by Stinissen et al., employing attenuated T cells autoreactive to multiple human myelin antigens. One of ordinary skill in the art at the time the invention was made would have been motivated to employ attenuated T cells autoreactive to multiple myelin antigens given the teachings of Stinissen et al. that MBP is not the only autoantigen candidate in MS, extended by Correale et al. that as MS develops, myelin breakdown exposes additional myelin antigens (besides MBP) to autoreactive T cells, thus broadening the autoimmune response, and the background teachings of the specification that multiple protein antigens are targeted in MS. One of ordinary skill in the art at the time the invention was made would also have been motivated to employ myelin proteins obtained from bovine as a convenient source of said proteins given the teachings of Correale et al. of the availability of said source. Further, the choice of dosage (Claim 17), and timing (Claim 16), would have fallen well within the purview of the skilled artisan at the time of the invention. Regarding the increasing of the dosages as set forth in Claims 18 and 19, one of ordinary skill in the art at the time the invention was made would have been well aware of the concept of increasing dosage if no response is obtained up to the point of efficacy or adverse reaction. These limitations do not render the claimed method patentably distinct.

Applicant's arguments filed 10/18/07 have been fully considered but they are not persuasive. Applicant argues that Stinissen et al. does not employ T cell lines in their method. A review of Figure 1 wherein the method is taught shows that T cell clones are developed which still can be considered to be T cell lines by the definitions of the National Cancer Institute (NCI) and Biology-Online.org.

Applicant argues that Stinissen et al. does not teach the treatment of secondary progressive MS.

The Background of the instant specification discloses that there are three basic types of MS: relapsing remitting (RR), secondary progressive (SP) and primary progressive (PP). The progressive diseases differ from the RR disease in that they no longer encompass the remitting stage. The progressive diseases differ from each other in that SPMS develops after RRMS whereas PPMS develops from the outset. Given the limited number of

types of MS, and their relationships to each other, it would be obvious to treat all types of MS with the same therapies and in particular, it would be obvious to treat either of the just two types of progressive disease with the same therapies.

Applicant argues a lack of expectation of success.

Applicant's argument is curious in view of the limited disclosure of limited (if any) success in the instant specification. A persuasive argument in this regard would necessitate a finding of a lack of enablement in the instant case.

Applicant again cites Van Der Aa et al. (2003). This time additionally arguing that Stinissen et al. teaches a "critical need" for T cell cloning in generating a T cell vaccine.

A review of the reference again discloses that the statement regarding the difficulty of generating T cell clones specific for three different myelin antigens is made in the Introduction section of the reference with no explanation. Indeed, the next paragraph teaches that the authors were able to do that very thing, i.e., the generation of sufficient T cells for vaccination, with no particular difficulty. Accordingly, the isolated statement regarding difficulty in generating T cell clones would not lead the skilled artisan to doubt the expectation of success with the claimed method. Additionally, Stinissen et al. did not teach any particular difficulty in establishing and expanding their T cell clones such that there would have been a lack of expectation of success.

Applicant further argues that Stinissen et al. teaches cloned T cells.

As set forth above, the cloned T cells of the reference can be considered to be the T cell lines of the claims. Regarding Claim 30, a combination of 2 or more T cell clones (as would be the T cells of the combined references) would comprise the T cells of Claim 30.

8. The following are new grounds for rejection necessitated by Applicant's amendment.

9. Claims 8, 9, 12, 14-19, 23, 26, and 28 are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, the T cell lines of Claim 8.

Applicant cites original pages 7 and 9-12 of the specification in support.

A review of the cites reveals that T cell lines are disclosed only at page 12. Said disclosure is then only in the context of Example 1 and thus appropriate only for the method of Claim 30.

10. No claim is allowed.

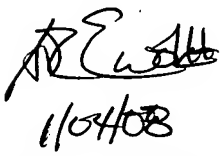
11. Applicant's amendment or action necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from

7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

13. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.



11/04/08

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